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Induction of apoptosis by troglitazone requires peroxisome proliferator-activated receptor gamma and ERK in lung cancer cells

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Troglitazone (TGZ), a synthetic PPAR gamma ligand, is able to induce cell growth arrest and apoptosis in human lung cancer cells, but its pathway is unclear. We therefore studied the role of ERK1/2 in NCI-H23 lung cancer cells treated by TGZ. We found that TGZ induced PPAR gamma and activated ERK1/2 accumulation in the nucleus, where the co-localization of both proteins was found and that the activation of ERK1/2 resulted in apoptosis via the mitochondrial pathway, reflected by the reduction of mitochondria membrane potential, change in Bcl-2 family members, release of cytochrome C into cytosol, and activation of caspase 9. Our study has demonstrated that TGZ induced apoptosis in lung cancer cells via a mitochondrial pathway, and this pathway was PPAR gamma- and ERK-dependent. The interaction between PPAR gamma and ERK may create an auto-regulatory and positive feedback loop to enhance the effect of ERK, whereas the activation of Akt may generate a negative feedback loop to control the degree of apoptosis which occurred in lung cancer cells. (Supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, CUHK 4390/03M).

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Human fetal development is necessary for leukocytic TLR maturation against bacterial infection

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TLR2 and TLR4 mainly respond to bacterial infections dependent upon their receptor and signal protein expression. Higher susceptibility of human neonates to bacterial infection compared to adults may be related to the deficiency of TLR2/4 or its adapter protein on mononuclear leukocytes. To understand this, we studied TLR2/4, MD2, MyD88, IRAK, JUK and NFκB expression using human mononuclear leukocytes (MNC) isolated from first and second trimester fetal liver, umbilical cord blood as well as adolescent peripheral blood. In this study, we compared lipopolysaccharide (LPS)-induced production of α-defensin from MNC and found TLR and MyD88 expression enhanced following the fetal maturation, while IRAK and NFκB expressions remained the same. Most interestingly, MD2 was undetectable in fetal liver MNC but expressed weekly in cord MNC and strongly in adolescent MNC cultures. In addition, only adolescent MNC increases the expression of TLR2/4, IRAK, NFκB and α-defensin after LPS exposure. LPS slightly increases TLR2/4 which express intensity in cord MNC culture, but not in fetal MNC cultures. Taken together, although TLR2/4 and its signals express in all MNC, the effect of LPS stimulation is mainly shown in the adolescent MNC cultures rather than in fetal leukocytes. TLR4 becomes a fully functional receptor against gram negative bacterial invasion dependent on the developmental courses. Lack of the MD2 may be responsible for fetal MNC immunodeficiency against the microbial infection due to failure of TLR4 binding to LPS. The gene controlling of MD2 expression deserves further study.

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Novel function of POSH, a JNK scaffold, as an E3 ubiquitin ligase for the Hrs stability on early endosomes

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POSH (plenty of SH3s) acts as a scaffold that links activated Rac1 and downstream c-Jun N-terminal kinase (JNK) signaling modules. However, it is unknown whether its functional-domain-mediated roles include the interesting RING-finger domain or its cellular function. Here, we provide evidence that subcellular localization of POSH is regulated by a particular domain of the protein and POSH was colocalized with hepatocyte-growth-factor-regulated tyrosine kinase substrate (Hrs) on early endosomes via interaction of Hrs with POSH's two rear SH3 domains. Moreover, the RING domain of POSH specifically regulates the stability of Hrs, but not of JNK1, via a ubiquitin–proteasomal degradation pathway. Finally, we demonstrate that JNK1 does not interact with Hrs under the conditions of POSH interacted with Hrs, but instead reduces the POSH-catalyzed ubiquitination of Hrs and their reciprocal interaction. Together, these data suggest that POSH has a distinct role as a specific E3 ubiquitin ligase for Hrs on early endosomes, and there exists a relationship between its separate activities as a scaffold and as an E3.

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The role of LPA signaling in development of the anterior nervous system

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We have been interested in the role of the signaling phospholipid lysophosphatidic acid (LPA) and its receptors in regulation of cell behaviors during development. The phospholipid LPA signals through G-protein-coupled receptors to